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# Multiple Beta-Sheet Molecular Dynamics of Two Abl-SH3 Domain Peptides

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Six parallelly placed ten stranded antiparallel  $\beta$ -sheets of DLSFMKGE (10x6xMK), and DLSFKKGE (10x6xKK) peptides, immersed in periodic water boxes, were subjected to molecular dynamics simulations (MD) for 90 ns and 40 ns respectively, to study the amyloid fibril formation tendencies of the two peptides. MD simulation showed that the 10x6xMK  $\beta$ -sheet stack is stable, but 10x6xKK  $\beta$ -sheet stack is not. 10x6xMK  $\beta$ -sheet is stable because of hydrophobic interactions of methionine-phenylalanine and leucine of the neighbouring sheets. Met, Phe, Leu make a hydrophobic core for the stack of  $\beta$ -sheets. During MD run the Met, Phe, Leu of neighbouring sheets act as conformational switch moving  $\beta$ -sheets by two amino acid step towards each other.

## 1 Introduction

Short protein sequence stretches drive the protein aggregation in amyloid fibrils<sup>1-3</sup>. Based on a homology search we have identified an aggregation-prone region in the Abl-SH3 domain of *Drosophila* with sequence DLSFMKGE (MK), and less amyloidogenic human homologous region with sequence DLSFKKGE (KK). The antiparallel flat  $\beta$ -sheets consisting of ten strands of MK and KK were constructed. We created two multi-sheet systems: (1) six parallelly placed 10-strand  $\beta$ -sheets of MK (10x6xMK) (Fig.1a), (2) six parallelly placed 10-strand  $\beta$ -sheets of KK (10x6xKK) (Fig.2a). Each of these  $\beta$ -sheet systems was surrounded by a 10 Å layer of water molecules over the solute and subjected to molecular dynamics (MD) simulations with the Amber 8.0 force field in the NPT (constant number of molecules, pressure, and temperature) scheme. The MD simulations were started from the temperature of 10 K and the temperature was gradually raised by the step of the ten degrees till 300 K, then the simulations were run at the constant temperature of 300 K. The 10x6xMK system was simulated by 90 ns of MD, the 10x6xKK system was simulated by 40 ns of MD.

## 2 Results

The 10x6xMK system maintains  $\beta$ -sheets, and the  $\beta$ -sheets remained together in a stack during all the time of MD simulation (Fig.1) and showed strong hydrogen bonding (Fig.3). During the simulation the  $\beta$ -sheets of the 10x6xMK system shifted towards each other by

two amino acids (Fig.1b, Fig.1c). The 10x6xKK system maintains  $\beta$ -sheets, but  $\beta$ -sheets do not remain together, they are hanging by a thread (Fig.2b), and moving away each from other (Fig.2c).

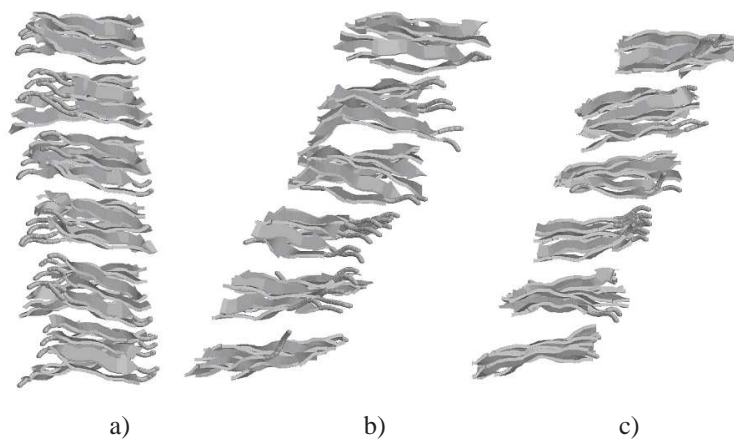


Figure 1. Multisheet system of DLSFMKGE peptides (10x6xMK) keeps together all the time of MD simulation. The 10x6xMK system at a) 351 ps, b) 21705 ps, c) 74499 ps of MD.

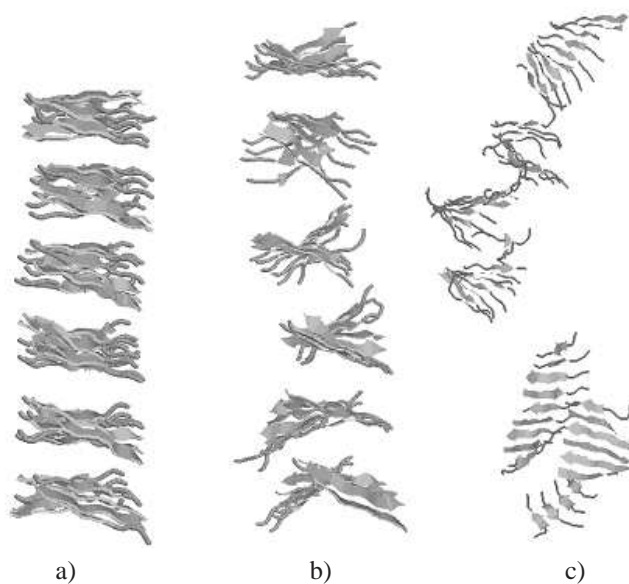


Figure 2. Multisheet system of DLSFKKGE peptides (10x6xKK) does not remain together during MD simulation. The 10x6xKK system at a) 382 ps, b) 11408 ps, c) 36771 ps of MD.

### 3 Conclusions

The MD simulation of multisheet systems revealed that: 1. The 10x6xMK  $\beta$ -sheet stack is stable, but the 10x6xKK  $\beta$ -sheet stack is not. 2. The 10x6xMK  $\beta$ -sheet is stable because of hydrophobic interactions of methionine and phenylalanine side chains and the leucine side chain of the neighbouring sheets. Met, Phe, Leu make a hydrophobic core for the stack of  $\beta$ -sheets. 3. During the MD run, the Met, Phe, and Leu residues of neighbouring sheets act as a conformational switch moving the  $\beta$ -sheets by two amino acid step towards each other. 4. Replacement of Met by Lys destroys the hydrophobic core, which is the stability factor of the  $\beta$ -sheets stack. The 10x6xKK system maintains  $\beta$ -sheets, but loses interactions between  $\beta$ -sheets. 5. The calculations of six  $\beta$ -sheets confirm the conclusion drawn for single sheet systems: parallelly placed  $\beta$ -sheets stabilize each other.

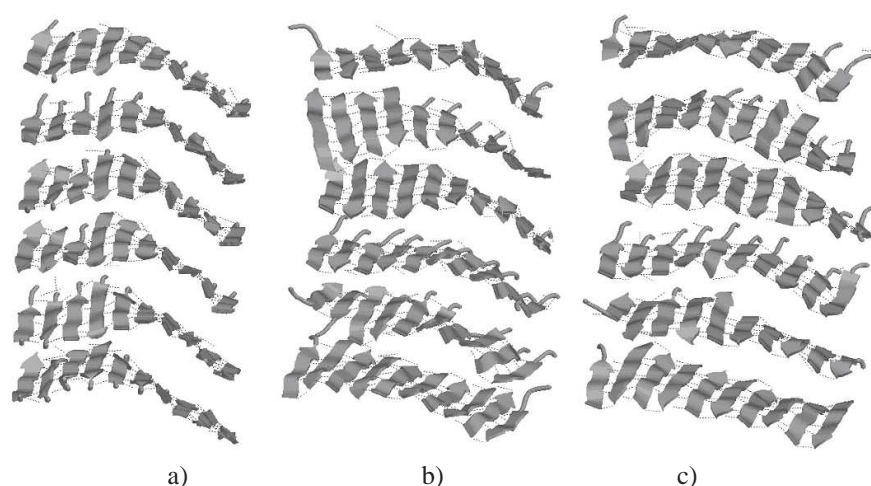


Figure 3. DLSFMKGE peptides (10x6xMK) show strong hydrogen bonding during the all MD run: a) 351 ps, b) 21705 ps, c) 74499 ps.

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